REMARKS

Claims 60 to 64 and 66 to 72 are pending. All pending claims have been rejected. Applicants have amended claims 64 and 67. No new matter is presented. In view of the foregoing amendments and the following remarks, Applicants respectfully request consideration.

35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 64 and 67 under 35 U.S.C. §112, second paragraph as being indefinite. Applicant respectfully requests reconsideration.

The Examiner states that "it is unclear from the claims whether the regulation of lysosomal pH is obtained upon the administration of a lysosomal UCP inhibitor (such as a dominant negative lysosomal UCP) in combination with a lysosomal targeted peptide or molecule, or alternatively upon the administration of a lysosomal targeted peptide or molecule in the absence of a lysosomal UCP inhibitor." As explained in the specification on page 4, lines 28 to 31, and page 8, line 30 to page 9, line 6, in some embodiments the lysosomal UCP inhibitor is a UCP binding peptide or molecule. In other embodiments, the UCP inhibitor is a UCP antisense or dominant/negative UCP inhibitor. Although Applicant believes the claims are definite, Applicant has amended claims 64 and 67 to clarify that the lysosomal UCP inhibitor is selected from the group consisting of a dominant negative lysosomal UCP, a lysosomal targeted binding peptide, and a lysosomal targeted binding molecule. This amendment does not alter the scope of the claims.

For the foregoing reasons, Applicant believes that claims 64 and 67 are definite and requests withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 60 to 64 and 66 to 72 under 35 U.S.C. §112, first paragraph, as not enabled. Applicant respectfully traverses this rejection.

The Examiner asserts that the specification is not enabled because "no evidence has been provided in the instant specification that the predictable regulation of lysosomal pH is achieved

upon inhibition of UCP function in lysosomes." Additionally, the Examiner asserts that the specification does not provide guidance for the successful treatment or prevention of infectious diseases.

Another reason provided in the Office Action for lack of enablement is that "Applicants have not provided guidance in the specification toward a method of regulating lysosomal pH in cells in vitro or in vivo comprising the administration of a lysosomal UCP inhibitor, nor of preventing or treating an infectious disease comprising the administration of a lysosomal UCP inhibitor."

The Examiner's reliance in objecting to the specification and claims upon a purported failure of the specification to disclose particular guidance for the delivery of active agents, is misplaced for at least the following reasons.

The specification provides guidance with respect to the identification of lysosomal UCP inhibitors (e.g., p. 49), a description of the relationship between lysosomal pH, UCP expression, and antigen presentation and processing (e.g. p. 48), examples of methods of assessing lysosomal membrane potential (e.g., p. 47), preferred routes of administration of the compounds of the invention (e.g., p. 71-74), and examples of delivery formulations and dosages (e.g., p. 59-67).

Additionally, Applicant has provided actual working examples which demonstrate the presence of UCP in lysosomal membranes and the ability to regulate the expression of lysosomal UCP using a lysosomal UCP inhibitor (e.g., Examples 6 and 7).

Further, Applicant submits herewith a declaration describing the findings described in a recent article by Arsenijevic *et al.* (Arsenijevic *et al.*, Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production, *Nature Genetics*, 2000, 26(4):387-8. Applicant has cited this reference in an IDS dated May 15, 2001.). Applicant provided evidence in the specification as filed that UCP was expressed in lysosomal membranes and that this expression could be altered using a lysosomal UCP inhibitor such as tunicamycin. The Arsenijevic *et al.* reference shows that the inhibition of UCP using knockout animals is useful to treat or prevent infectious disease.

Arsenijevic *et al.* demonstrate a relationship between uncoupling protein-2 (UCP2) expression and both the limitation of reactive oxygen species (ROS) and macrophage-mediated immunity. Arsenijevic *et al.* found that compared to wildtype mice, $UCP2^{-/-}$ (knockout) mice resisted and eliminated infectious challenge more efficiently. They believe the macrophages of the knockout mice have a greater capacity to generate ROS, which is consistent with observations of decreased UCP2 mRNA concentrations associated with increased ROS and increased UCP2 mRNA concentrations associated with decreased ROS. Accordingly, the Arsenijevic *et al.* data demonstrate that decreasing UCP function (by eliminating the UCP2 gene) is useful to prevent or treat infection.

However, Arsenijevic *et al.* did not recognize that UCP was expressed in the lysosome. Based on the finding of the invention by Applicant that UCP is expressed in lysosomes, the teachings of Arsenijevic *et al.* can be interpreted to mean that loss of lysosomal UCP expression is associated with the ability to treat or prevent infection. Since the infection-resistant knockout mice made by Arsenijevic *et al.* did not express lysosomal UCP, the lysosomes would have decreased pH compared to those of wildtype mice. Therefore, Applicant believes that the regulation of lysosomal pH by, for example, the administration of a UCP lysosomal inhibitor, would be useful to treat or prevent infectious disease.

Thus, the Arsenijevic *et al.* reference confirms that inhibition of UCP is useful for treating infectious disease. Applicant believes the claims are enabled, and respectfully requests withdrawal of the rejection of claims 60 to 64 and 66 to 72 under 35 U.S.C. §112, first paragraph.

Applicant respectfully requests reconsideration of the pending claims in view of the amendments and reasoned statements made above. Applicant has provided Information Disclosure Statements dated August 2, 2000, October 31, 2000, and May 15, 2001, and respectfully requests that the Examiner consider the references cited and initial and return the PTO-1449 forms. If the Examiner wishes to advance the prosecution in any way, or if the amendment is unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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Marked-Up Version of Pending Claims

(All pending claims are presented for the Examiner's convenience.)

60. (Unchanged) A method for regulating lysosomal pH, comprising: modifying lysosomal UCP activity in a cell to regulate lysosomal pH.

61. (Unchanged) The method of claim 60, wherein the cell is a T cell.

62. (Unchanged) The method of claim 61, wherein the cell is a neutrophil.

63. (Unchanged) The method of claim 61, wherein the lysosomal UCP activity is modified by contacting the cell with a lysosomal UCP inhibitor.

64. (Amended) The method of claim 63, wherein the lysosomal UCP inhibitor is selected from the group consisting of a dominant negative lysosomal UCP, [and] a lysosomal targeted binding peptide, and a lysosomal targeted binding [or] molecule.

66. (Unchanged) A method for treating or preventing an infectious disease, comprising: administering to a subject having or at risk of developing an infectious disease a lysosomal UCP inhibitor in an effective amount for treating or preventing the infectious disease.

67. (Amended) The method of claim 66, wherein the lysosomal UCP inhibitor is selected from the group consisting of a dominant negative lysosomal UCP, [and] a lysosomal targeted binding peptide, and a lysosomal targeted binding [or] molecule.

68. (Unchanged) The method of claim 66, further comprising administering an antigen to the subject.

69. (Unchanged) The method of claim 68, wherein the antigen is selected from the group consisting of a viral, a bacterial, a parasitic, and a fungal antigen.

70. (Unchanged) The method of claim 66, wherein the subject is infected with an intracellular pathogen.

71. (Unchanged) The method of claim 70, wherein the intracellular pathogen is an intracellular bacteria.

72. (Unchanged) The method of claim 70, wherein the intracellular pathogen is an intracellular parasite.